REQUEST FOR CORRECTION OF THE EPA'S 2010 IUR FOR CHLOROPRENE

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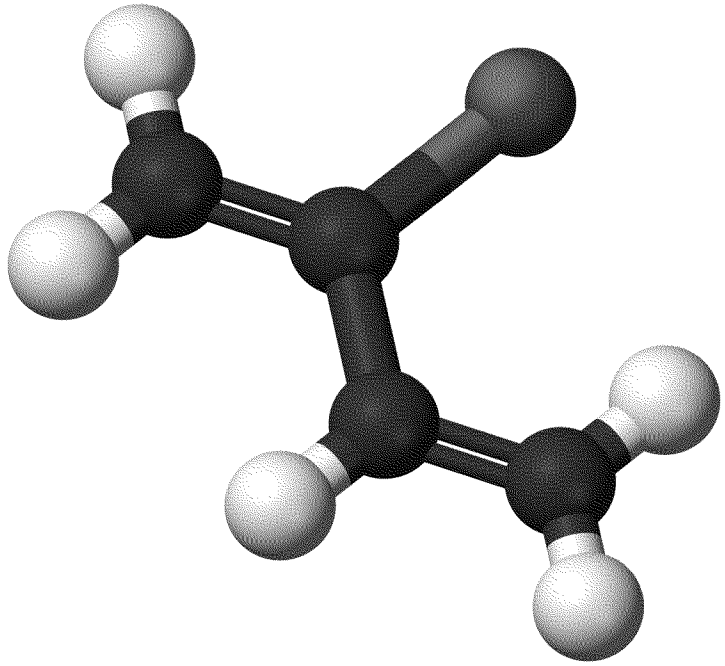


RAMBOLL ENVIRON

EXECUTIVE SUMMARY 1

- EPA published the IRIS Toxicological Review of Chloroprene in 2010, with an inhalation unit risk (IUR) of 5×10^{-4} per $\mu g/m^3$.
- This is the 5^{th} highest IUR derived by IRIS for any chemical classified by IARC as carcinogenic (Group 1) or probably carcinogenic (Group 2a).
- IARC classified chloroprene as possibly carcinogenic (Group 2b).
- Ramboll Environ was requested to conduct a detailed review of the 2010 IRIS, and to derive an IUR for Chloroprene.

EXECUTIVE SUMMARY 2

- **Key Findings: All lines of evidence indicate that the IUR should be corrected:**
- The highest quality epidemiological studies demonstrated no excess lung or liver cancer risk.
- Toxicological data do not support a mutagenic mode of action.
- Multiple lines of evidence indicate large differences across species.
- Using NRC best practices recommendations, EPA methods and pharmacokinetic data, the Ramboll Environ IUR is 156 times lower than the 2010 IRIS IUR.
- Cancer risk estimates based on the Ramboll Environ IUR are consistent with the epidemiological data.

INTRODUCTION

- EPA published the IRIS Toxicological Review of Chloroprene* in 2010, with an inhalation unit risk **(IUR) of 5 x 10^{-4} per $\mu g/m^3$.**
- Denka Performance Elastomer (DPE) acquired the Neoprene production facility in LaPlace, Louisiana from DuPont on November 1, 2015.
- On December 17, 2015, EPA published the 2011 National Air Toxics Assessment (NATA), including a risk assessment based on the facility's emissions and the 2010 IRIS IUR.
- The NATA study identified DPE's facility as associated with **one of the highest offsite cancer risks** of any chemical facility in the US.
- DPE retained Ramboll Environ to evaluate the scientific validity of the 2010 IRIS IUR.
- Using EPA standard methods and publicly available data, Ramboll Environ determined that the 2010 IRIS **IUR is overestimated by a factor of 156**.

* U.S. Environmental Protection Agency, Washington, DC, EPA/635/R-09/010F, 2010.

OBJECTIVES

- Evaluate the 2010 IRIS Review of Chloroprene, especially the IUR, in light of NRC (2011, 2014) guidance on improving IRIS assessments:
  - How studies are evaluated: quality assessment and weighting
  - Better integration of data across all lines of evidence
- Critically review and integrate the published epidemiological, toxicological, and mode of action evidence on chloroprene carcinogenicity.
- Apply a standard pharmacokinetic correction to the chloroprene IUR.
- Provide a "reality check" for the IUR.

EPIDEMIOLOGICAL EVIDENCE

COMPARISON OF KEY CRITERIA ACROSS STUDIES

Key Criteria	US and Europe (Marsh *et al.* 2007)	Armenia (Bulbulyan *et al.* 1999)	Russia (Bulbulyan *et al.* 1998)	China (Li *et al.* 1989)
Sample Size	12,430	2,314	5,185	1,258
Follow-up	1949–2000	1979–1993	1979–1993	1969-1983
Exposure Assessment	Exposure modeling – 7 categories	Index (none, low, high)- before/after 1980	Index (none, med, high)- IH (inadequate) + job	High vs. low based on recall
Baseline rates	National, local plant area counties 1960–1994	Armenian rates 1980-1989	Moscow rates 1979–1993 or 1992–1993 (liver)	From "local area" 1973–1975 expected lung cancers: 0.4
Confounding	Used local rate comparisons; Low prevalence of other liver cancer risk factors	Alcohol use (high cirrhosis rates) and smoking prevalent	Alcohol use (high cirrhosis rates) and smoking; Co-exposure to VC	Hepatitis B and aflatoxin; Co-exposures to VC

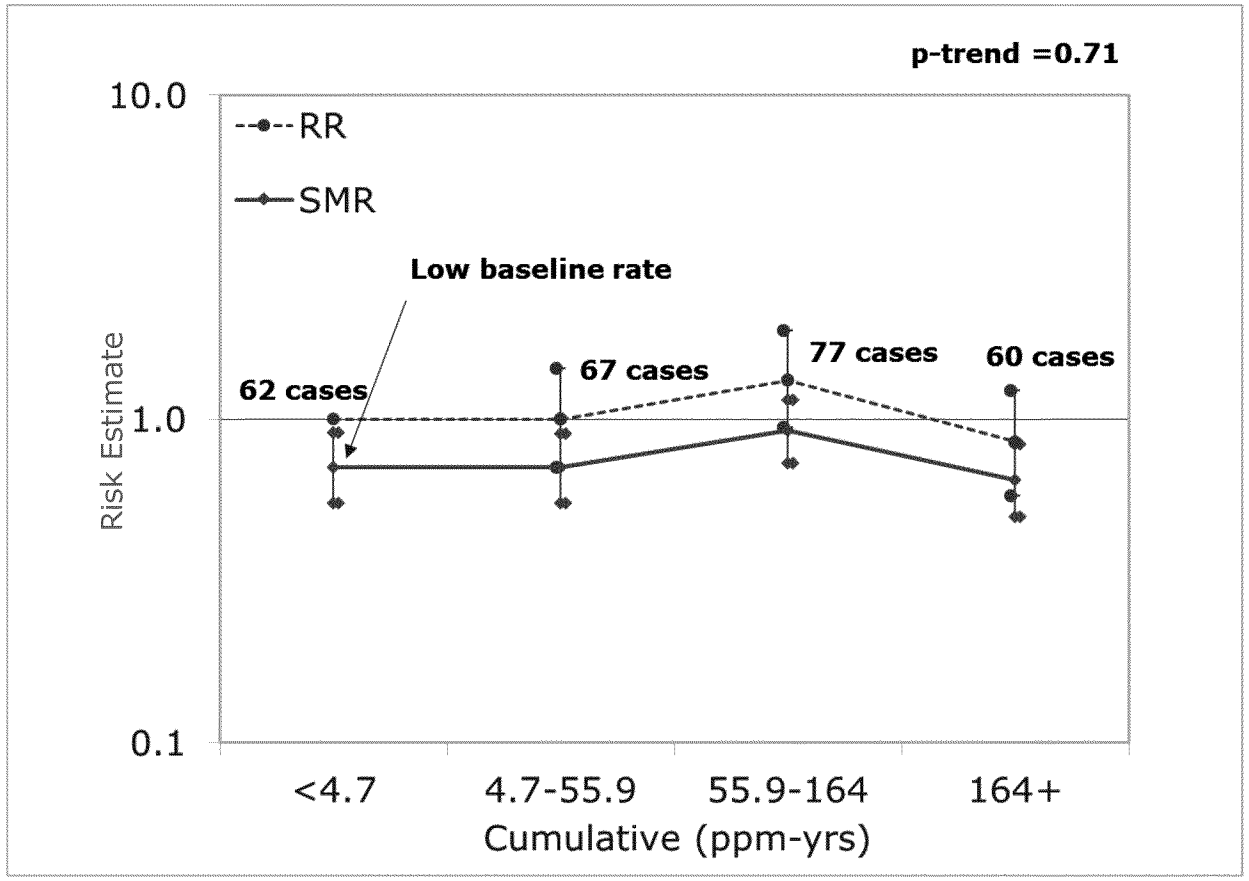
MARSH STUDY RECEIVES HIGHEST QUALITY RANK

US EPA Criteria	Marsh et al. (2007 a,b) Study				Other Studies			
	Kentucky[1]	North Ireland	Louisiana[1]	France-Mortality[1]	Armenia[2]	France-Incidence[3]	Russia[4]	China[5]
Clear objectives	H‡	H	H	H	H	H-M	H	M
Comparison groups	H	H-M	H-M	M	M	M	M-L	L
Exposure	H	H	H	H	M	M	L	L
Follow-up	H	H-M	H	H-M	M-L	M-L	M-L	M-L
Case ascertainment	H	H-M	H-M	H-M	M	M	M	H-M
Control of bias	H-M	H-M	H-M	M	M-L	M	M	M-L
Sample size	H	H	M	L	M-L	L	H-M	M-L
Data collection and evaluation	H	H	H	H	M	M	M-L	M-L
Adequate response	H	H	H	H	M	M	M	H-M
Documentation of results	H	H	H	H	M-L	M	M	L
Overall rank (1=best)	**1**	**2**	**3**	**4**	**5**	**5**	**5**	**6**

Source: Bukowski 2009 ‡ Subjective estimate of study quality for each specific criterion H=high, M=medium, L=low; 1 – Marsh et al. 2007; 2 – Bulbulyan et al. 1999; 3 – Colonna and Laydevant 2001; 4 – Bulbulyan et al. 1998; 5 – Li et al. 1989

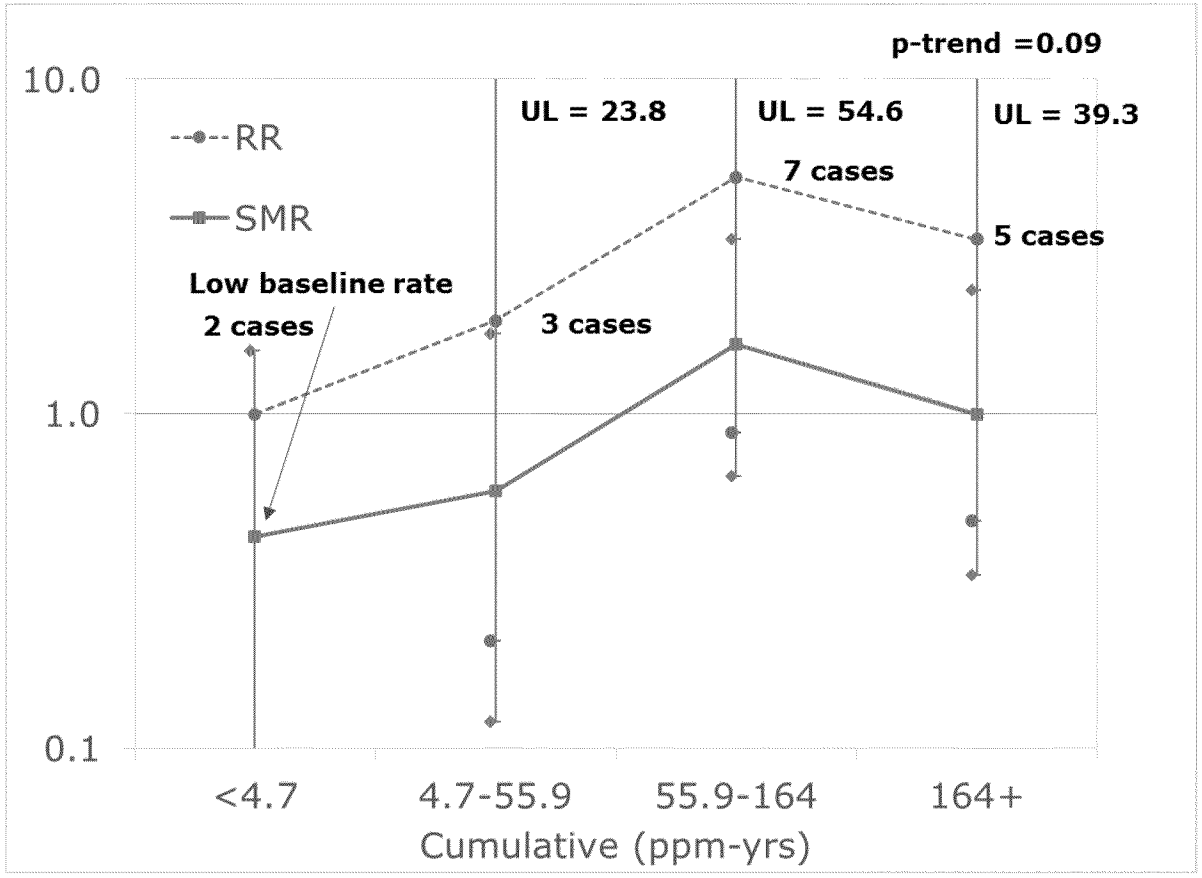
MARSH STUDY SHOWS NO INCREASED LUNG OR LIVER CANCER RISKS

Respiratory cancers RRs and SMRs by cumulative chloroprene exposure, Louisville plant



Source: Marsh 2007b

Liver cancers RRs and SMRs by cumulative chloroprene exposure, Louisville plant



Source: Marsh 2007b

LOCAL COMMUNITY-LEVEL CANCER RATES

- Cancer incidence data from the Louisiana Tumor Registry for St. John the Baptist Parish (where DPE plant is located) and for the state of Louisiana
- Five most recent years

Cancer site	Parish Rate	State Rate	Ranking (1=lowest cancer rate)
All cancers	463.2	478.7	15/64
Respiratory cancers	60.1	70.5	7/64
Liver cancers	< 3 cases (too few to report)		Unknown*

*Unknown as as there were 28 parishes with too few liver cancer cases

Source: https://statecancerprofiles.cancer.gov/incidencerates/index.php?stateFIPS=22&cancer=001&race=00&sex=0&age=001&type=incd&sortVariableName=rate&sortOrder=default#results

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OCCUPATIONAL CANCER RATES IN THE PONTCHARTRAIN FACILITY, LA

- Marsh et al. (2007a) results for 1,357 workers at the Pontchartrain facility in LA (US and local reference rates)

Cancer site	US-based SMR	Local-based SMR
All cancers	0.74 (0.51-1.04)	0.68 (0.47–0.95)
Respiratory cancers	0.72 (0.37-1.26)	0.62 (0.32-1.09)
Liver cancers	None reported	None reported

MARSH ET AL. (2007) CONCLUSION

Marsh et al. (2007) should be given greater weight than studies from Asia, Russia and Armenia:

"*We conclude that persons exposed to chloroprene or vinyl chloride at the levels encountered in the four study sites* ***did not have elevated risks of mortality from any of the causes of death*** *examined, including all cancers combined and* ***lung*** *and* ***liver*** *cancer, the cancer sites of a priori interest."*

"This ***conclusion is corroborated by our detailed analyses of mortality*** *in relation to* ***qualitative and quantitative exposures to CD*** *and VC at each of the four study sites."*

Source: G.M. Marsh et al. / Chemico-Biological Interactions 166 (2007) 285–300

TOXICOLOGICAL EVIDENCE

ANIMAL STUDIES

- Studies conducted in B6C3F1 mice and Fischer rats (NTP, 1998), and in Wistar rats and Syrian hamsters (Trochimowicz et al., 1998) at chloroprene concentrations ranging from 10 to 80 ppm.
- A significant incidence of tumors seen across many organ sites, primarily in mice and at the highest exposure levels.
- The most sensitive species/tumor site is the female mouse and the lung.
- Fewer tumors in Wistar rats and Syrian hamsters; little consistency across species both in the number of tumors and in tumor location.
- Differences in tumor incidence can be explained by using PBPK modeling and the calculated internal dose of metabolized chloroprene.

SUMMARY OF ANIMAL DATA (DERIVED FROM HIMMELSTEIN ET AL. 2004)

Species	Exposure concentration (ppm)	PBPK internal dose (mg/g)	Lung tumor incidence	Number of animals
Syrian Hamster (Trochimowicz et al., 1998)	0	0	0	100
	10	0.18	0	97
	50	0.88	0	97
Wistar rat (Trochimowicz et al., 1998)	0	0	0	97
	10	0.18	0	13
	50	0.89	0	100
Fischer rat (NTP, 1998)	0	0	3	50
	12.8	0.22	3	50
	32	0.55	6	49
	80	1.37	9	50
B6C3F1 mouse (NTP, 1998)	**0**	**0**	**15**	**50**
	12.8	**3.46**	**32**	**50**
	32	**5.3**	**40**	**50**
	80	**7.18**	**46**	**50**

In vitro mutagenicity results are inconsistent

Study	Method	Exposure	Response
Bartsch *et al*., 1979	Desiccator	4 hours	+
Westphal *et al*., 1994	Pre-incubation	2 hours	-
NTP, 1998	Pre-incubation	20 min.	-
Willems, 1980	Desiccator	24-48 hours	+

In vivo results are mostly negative, and mutagenicity profile is different from 1,3-butadiene

Chemical	*In Vivo* (B6C3F1 mouse)		
	CA	**SCE**	**MN**
Chloroprene	-	-	-
1,3 - Butadiene	+	+	+

CA – chromosome aberrations; SCE - sister chromatid exchange;MN - micronucleus test; Source: Tice 1988

Weight of evidence is not consistent with a mutagenic MOA. An alternative MOA should be considered in accordance with EPA and NRC guidelines.

CHLOROPRENE IUR

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Compound (Year of Review)	IUR per ug/m^3	Basis	PBPK adjustment	Classification	Ratio
Chloroprene (2010)	**5×10^{-4}**	Multiple tumors in mice, mutagenic MOA	No	Possibly Carcinogenic	1
1,3 Butadiene (2002a)	3×10^{-5}	Human occupational studies	No	Known Carcinogen	~20
Benzene (2002b)	2×10^{-6} – 7.8×10^{-6}	Human occupational studies	No	Known Carcinogen	250
Vinyl Chloride (2000)	4.4×10^{-6}	Liver tumors in rats	Yes	Known Carcinogen	~100

Adjusted IUR of chloroprene is more in line with other known carcinogens; e.g., VC IUR is based on animal data, but with PBPK model adjustments.

UNCERTAINTIES IN THE 2010 IUR

Step	IUR per ug/m^3	Basis
Most sensitive endpoint/species (portal-of-entry DAF=1.7)	1.06×10^{-4}	Lung tumors in female mice as a portal-of-entry effect
Most sensitive endpoint/species (systemic lesion DAF=1)	1.81×10^{-4}	Lung tumors in female mice as a systemic effect
Multiple tumor adjustment	2.7×10^{-4}	Multiple tumors
Rounding	3×10^{-4}	Rounding
Application of ADAF	**5×10^{-4}**	Adjustment (assuming mutagenicity)

PHARMACOKINETIC CORRECTION OF THE ANIMAL DATA

	IUR per ug/m^3	Basis	Resulting decrease in IUR
US EPA (2010)	**5 x 10^{-4}**	Fully adjusted composite value in female mice with ADAF correction	Referent
Allen et al. (2014)	1.86 x 10^{-6}	PBPK dosimetric adjustment of lung tumors in female mice in target organ; includes animal and human data	~250 fold decrease
Ramboll Environ (2017)	3.2 x 10^{-6}	PBPK dosimetric adjustment of lung tumors in female mice in the target organ; based on animal data only	156 fold decrease

PHARMACOKINETIC CORRECTION OF THE CHLOROPRENE IUR

- PBPK model was published by Himmelstein et al. (2004).
- Data were provided to EPA at the time of the review to check the validity of the model; however, EPA did not incorporate these data into the final IUR estimate.
- Data provided to EPA have been published (Yang et al., 2012; Thomas et al., 2013).
- Allen et al. (2014) reported that an IUR that incorporates pharmacokinetic differences 250 times lower than the 2010 IRIS IUR.
- Using the internal dose estimates from PBPK modeling from Yang et al. (2012) Ramboll Environ derived an IUR of **3.2×10^{-6}** per $\mu g/m^3$ which is **156 times lower** than the 2010 IRIS IUR.

"REALITY CHECK"

Source	Unit Risk (per ppm)	Mean Exposure* (ppm)	Excess Cancers (Risk Estimate)	Excess Cancers (Observed–Expected) Local referent
US EPA (2010) lung tumor	0.65	8.42	5.5	-84 (lung)
multi tumor	1.08	8.42	9.1	-1.9 (liver)
w/ADAF	1.80	8.42	15.2	
Allen et al. (2014) lung tumor	0.0067	8.42	0.06	
Ramboll Environ lung tumor	0.012	8.42	0.1	

*Mean exposure reported by Marsh et al. 2007a

IUR corrected for pharmacokinetic differences results in a cancer risk estimate consistent with epidemiological results (i.e., no observable excess risk).

CANCER CLASSIFICATION

CANCER CLASSIFICATION OF CHLOROPRENE

EPA classified chloroprene as "likely to be a human carcinogen" based on:

- National Toxicology Program (NTP, 1998) chronic inhalation bioassay;
- Associations between chloroprene exposure and liver cancer in four of nine epidemiological studies;
- Limited evidence of lung cancer;
- Proposed mutagenic mode of action; and
- Analogies with 1,3-butadiene and vinyl chloride

Critical review of the evidence indicated that four of these five cannot be substantiated.

The classification should be revisited and a clearer narrative provided.

https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=1021

SUMMARY AND CONCLUSIONS

BASES FOR A REQUEST FOR CORRECTION OF THE 2010 IUR

- The highest quality epidemiological studies do not demonstrate a causal relationship between occupational exposures to chloroprene and cancer.
- Many lines of evidence point to pharmacokinetic differences across species.
- PBPK modelling is the best approach for correcting the IUR because of large pharmacokinetic differences between the mouse and humans.
- Using PBPK model output and standard EPA methods, Ramboll Environ calculated an IUR that is 156 times lower than the 2010 IRIS IUR.
- The IRIS classification of chloroprene as "likely to be a human carcinogen" should be reclassified given our understanding of the MOA.

Integration of the full body of evidence indicates that the pharmacokinetic differences between the mouse and humans require that the IUR be corrected using PBPK model results.

THANK YOU

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